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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/163,289	09/29/1998	HARRY C. DIETZ	JHU1400-1	9819

7590

05/06/2003

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EXAMINER

SCHMIDT, MARY M

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 05/06/2003

28

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/163,289

Applicant(s)

DIETZ, HARRY C.

Examiner

Mary M. Schmidt

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 14 February 2003
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-13 and 15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-13 and 15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on 29 September 1998 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 25
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: See Continuation Sheet.

Continuation of Attachment(s) 6). Other: See the PTO-948 provided with the Office action mailed 7/30/02 for the drawing corrections needed.

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DETAILED ACTION

Information Disclosure Statement

1. Two copies of the IDS having the Sontheimer, Abounader and Montgomery references have been received. A signed copy of the one filed 2/14/03 is provided and the one filed 1/21/03 has been crossed through as a duplicate.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims) recite the functional language for the claimed compositions "wherein the antisense nucleic acid is capable of having activity and is flanked by the stem loop structures...." The claims are considered indefinable for the language "capable of having activity" since the metes and bounds of the claimed activity is not clearly defined in the specification as filed. The specification as filed refers to suppression of gene expression using the antisense constructs, but the language "activity" embraces a breadth of actions not limited to suppression. For example, the antisense may bind the target gene, but not suppress it, and the

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action of binding would be considered an "activity." Since the specification as filed has not further defined other activities than suppression as the function of the claimed antisense constructs, one skilled in the art would not understand the metes and bounds of other "actions" that the claimed constructs would have, and thus one skilled in the art would not understand the metes and bounds of the claimed antisense constructs from the functional language.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons of record set forth in the Office action mailed 7/30/02.

Applicant's arguments filed 2/14/03 have been fully considered but they are not persuasive.

Claim 1 was amended to state that there is a proviso that the antisense nucleic acid is not within the 5' or 3' stem loop structures.

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This amendment has not affected the instant rejection since the grounds for rejection remain that applicant was not considered in possession of a representative number of species of the claimed nucleic acid constructs at the time the invention was made.

Applicant states that they are in possession of "antisense constructs flanked by 5' and 3' U1 snRNA stem loop structures." However, the claims are not limited to flanking with 5' and 3' U1 snRNA structures but are broadly drawn (also in view of the open "comprising" language) to a broad genus of possible nucleic acid constructs having 5' and 3' stem loop structures of any nucleic acid composition, the breath of which is not adequately described by the specification as filed. The applicant points to the specification on page 7, lines 12-23 and page 8, lines 18-25 to describe the breath of constructs in claim 1. However, in this section, the specification portrays the elements very broadly, for example on page 8, lines 5-6: "Virtually any combination of stem loop structure is envisioned in the construct of the invention." Thus the specification does not serve to further define the breath of the claimed constructs nor provide substantial written description support for such a breath as "virtually any combination of stem loop structures".

Applicant further states that "the U1 snRNA stem loops are set forth for exemplary purposes only. The requirements for functionally equivalent stem loops are clearly and coherently disclosed in the specification... which also describes a U3 stem loop structure as an alternative. Based on this disclosure, it is submitted that those skilled in the art could readily determine functional equivalents to the U1 snRNA stem loops."

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In response, the claims are not limited to U1 snRNA stem loops or U3 stem loops alone. Instead the claims are limited to use of virtually any stem loop combination. As such, even though the sequence of U1 snRNA and U3 stem loops was known in the art at the time the invention was made, one skilled in the art would not have been able to envisage a representative number of species of the genus of the instantly claimed invention due to the extreme breath of the instant invention drawn to use of virtually any combination of stem loops.

Applicant further states that "[t]hose skilled in the art recognize that the antisense nucleic acid can be directed toward any target nucleic acid. Therefore, any antisense nucleic acid which includes sequences capable of activity, i.e., hybridizing with its complementary target and affecting expression of that target can be used in invention constructs. For example, antisense sequences can be directed to the 5' or 3' termini of the target message, to splice junctions, or to internal sequences. Clearly, those skilled in the art would readily be able to determine which sequences are appropriate antisense nucleic acids to utilize in an invention construct."

In response, while it was fairly routine at the time the invention was made to screen for at least one antisense sequence to a known target gene, such knowledge did not allow one skilled in the art to determine the target gene sequence envisioned by the instant invention. Since the target gene is a major consideration in design of antisense, and since the specification as filed has not provided a representative number of species of target genes, one skilled in the art would not have been able to readily envisage a representative number of species of the claimed invention. Furthermore, this aspect of the rejection is in view of the above comments since the antisense

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portion of the claimed constructs is necessarily flanked by some sort of stem loop structures. It is thus not clear what antisense nucleic acid constructs would necessarily be flanked by stem loop structures for the purposes of the claimed invention. Without further guidance in either the specification or the prior art, one of skill in the art would not have recognized that application was in possession of a representative number of species of the claimed invention at the time the invention was made.

6. Claims 1-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid constructs for suppressing gene expression comprising the 5' stem loop structure, antisense nucleic acid, 3' stem loop structure, where the antisense functions to suppress gene expression, does not reasonably provide enablement for the claimed nucleic acid constructs where the antisense is capable of having activities other than suppression of gene expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

See the 35 U.S.C. 112, second paragraph, rejection above.

The specification as filed teaches use of the claimed constructs for gene suppression but does not provide other types of activities that the claimed constructs may have.

The art teaches that antisense constructs are useful for decreasing gene expression, or suppressing gene expression, by the mechanism of binding to a target gene of complementary

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nucleic acid sequence, and facilitating degradation of the target sequence by nuclease action. The art does not teach that such antisense molecules are useful for other types of "activity" as instantly claimed. See Branch, Green and Ma for a description in the art of antisense oligonucleotides that are used for inhibition of gene expression. Since the breadth of "activity" in the instant claims is not defined in the specification as filed, the claim could embrace actions such as increase in gene expression. However, as taught in the art (Branch, Green and Ma), antisense is used for decreasing gene expression and not increasing gene expression. As such, one of skill in the art would necessarily practice an undue amount of experimentation to make and use the breadth of claimed constructs for the recited use of having any "activity" since antisense were only disclosed in the specification and known in the art to be useful for decreasing or suppression of gene expression activity.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Michienzi et al. for the same reasons of record as set forth in the Official Actions mailed 7/17/01, 8/29/00 and 7/30/02.

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Applicant's arguments filed 2/14/03 have been fully considered but they are not persuasive.

Claim 1 was amended to state that there is a proviso that the antisense nucleic acid is not within the 5' or 3' stem loop structures.

Applicants state that their invention "distinguishes over Michienzi by reciting a nucleic acid construct for suppressing gene expression comprising in 5' to 3' orientation, a 5' stem loop structure, an antisense nucleic acid, and a 3' stem loop structure, wherein the stem loop structures flank the antisense nucleic acid and with the proviso that the antisense nucleic acid is not within the 5' or 3' stem loop structures. While not wishing to be bound by a particular theory, it is believed that since the natural hairpins in U sn RNAs protect the molecules from rapid turnover (presumably by blocking the access of exonucleases), modified snRNAs might serve as excellent vehicles for regulatory sequences such as antisense, ribozymes, etc. Implicit in this approach is the need to place the regulatory sequence between the unaltered 5' and 3' hairpins-- not 5' to both hairpins or within either hairpin, as set forth in the prior art."

As explained above, the new proviso does not exclude the teachings of Michienzi since there is one full stem-loop clearly depicted in Michienzi on either side of the antisense construct. Thus, applicants assertion that the antisense in Michienzi is 5' to both hairpins or within either hairpin is incorrect. Furthermore, the claims are not limited to UsnRNA constructs such that a specific region of a U snRNA construct must be found on either side of the antisense construct. Michienzi supports applications assertion that U sn RNA constructs are useful for protecting

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antisense during delivery, and simultaneously shows in their figures that there are clearly two stem loops on either side of the antisense construct. A stem loop in this instance is a region of complementary binding and tertiary hairpin structure. The claims are not limited as to how many additional stem loops may be found in the claimed construct, and thus the teachings of Michienzi stand as prior art.

Applicant continues to assert that "Michienzi describes nucleic acid constructs in which the stem loop III of U1 snRNA is modified by the addition of a hammerhead ribozyme within the stem loop structure. Applicant's constructs contain unmodified stem loop structures which flank an antisense nucleic acid sequence, wherein the antisense nucleic acid sequence is an active sequence. The antisense sequences of Applicant's constructs are not contained within either of the stem loop structures."

As pointed out above, the instant specification as filed does not rule out use of "virtually any combination of stem loop structure ... envisioned in the construct of the invention." Thus, the presence of multiple hairpin stem loop structures in the U1 snRNA construct taught by Michienzi is not ruled out as an option in the instantly claimed invention.

Applicants further state that "Michienzi's allegedly unmodified U1-Rz construct is a U1 snRNA that has a hammerhead ribozyme nucleic acid sequence inserted into the stem-loop III nucleic acid sequence. Michienzi's modified construct (U1-Rzm) is a construct in which the nucleic acid sequence forming the catalytic core of the hammerhead, i.e., CUGAUGA, has C

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replaced by G.... Such modification renders the catalytic activity of the ribozyme inactive. In contrast, the antisense molecules as claimed in Applicant's invention are active molecules."

However, the instant specification as filed defines the "unmodified" stem loop structures as any stem loop wherein "the folding pattern of the stem loop structure is not compromised by alterations in the nucleic acid sequence of the naturally occurring molecule. For example, it is understood that alterations which include, but are not limited to, mutations, insertions, deletions and substitutions of one or more nucleotides can be made within the sequence of the stem loop, as long as the stabilization function and hairpin formation of the stem loop is maintained."

Therefore, the insertion of the ribozyme taught by Michienzi in the U1 snRNA sequence, is embraced by the definitions of "unmodified" in the instant specification (page 7) which actually allows for modifications in the unmodified stem loops so long as function is retained. Michienzi et al. did teach that function was maintained of the U1 snRNA stem loops. Further, the stem loops of the flanking U1 snRNA stems on either side of loop III, are unmodified. Therefore, all the claimed limitations are met for unmodified stem loops flanking the antisense/ribozyme in the teachings of Michienzi et al.

Thus, while it is understood that the U1-Rz construct referred to in Figure 1 of Michienzi et al. does have the ribozyme placed in stem-loop III of the U1 snRNA, this does not render the U1-Rz construct "modified" in view of Applicant's definition in the specification recited above. The figure clearly shows one flanking hairpin on either side of the ribozyme site that is unmodified.

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It is further understood that Michienzi's "modified" construct is the modification of the ribozyme, not the U1 snRNA, to make a construct having an inactive ribozyme as a control (the U1-Rz_m) construct in contrast to the "unmodified" U1-Rz constructs having functional ribozymes. However, as argued above, these "unmodified" constructs taught by Michienzi et al. are embraced by Applicant's definition of "unmodified" on page 7 of the instant specification.

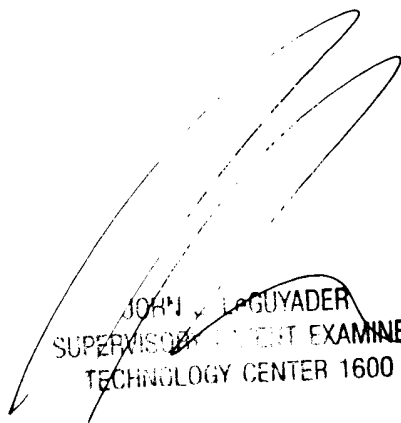
9. Claim 15 is considered free of the prior art since Michienzi et al. taught *X.laevis* cells injected with vectors expressing the HIV Rev gene (page 7220) and administering a modified and unmodified ribozyme U1 snRNA construct, but did not teach administration of a modified nucleic acid encoding a WT polypeptide corresponding to the gene product being suppressed wherein the modified nucleic acid is resistant to ribozyme cleavage and/or antisense inhibition as claimed.

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10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.


JOHN LE GUYADER
SUPERVISOR / EXAMINER
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M. M. Schmidt
May 4, 2003